CSIRO PUBLISHING

Full Paper

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2008**, *61*, 881–887

One-Pot Synthesis of 2-Substituted Benzoxazoles Directly from Carboxylic Acids

Dinesh Kumar,[A] *Santosh Rudrawar,*[A] *and Asit K. Chakraborti*[A,B]

[A]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S. A. S. Nagar, Punjab 160 062, India.

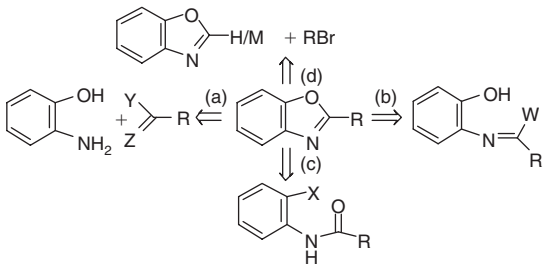
[B]Corresponding author. Email: akchakraborti@niper.ac.in

Methanesulfonic acid has been found to be a highly effective catalyst for a convenient and one-pot synthesis of 2-substituted benzoxazoles by the reaction of 2-aminophenol with acid chlorides, generated in situ from carboxylic acids. Aryl, heteroaryl, and arylalkyl carboxylic acids provided excellent yields of the corresponding benzoxazoles. The reaction conditions were compatible with various substituents such as chloro, bromo, nitro, methoxy, cyclopentyloxy, phenoxy, thiophenoxy, and conjugated double bonds. Benzoxazole formation was found to be general with respect to substituted 2-aminophenols.

Manuscript received: 6 May 2008.
Final version: 14 September 2008.

Introduction

Compounds bearing the benzoxazole moiety exhibit a broad spectrum of biological activities, for example, melatonin[1,2] and the 5-HT3 receptor agonist,[3] the VLA-4 antagonist,[4] inhibitors of various enzymes involved in the pathophysiology of different diseases (e.g., fructose-1,6-bisphosphatase,[5] kinases,[6,7] HIV-1 reverse transcriptase,[8] LPAAT-β,[9] cyclooxygenase,[10] and elastase[11]), anticancer,[12,13] antimycobacterial,[14–16] antimicrobial, and manopeptimycin glycopeptide antibiotics.[17–20] Thus, the benzoxazole moiety has earned the status of a versatile pharmacophore. Benzoxazoles are also used as fluorescent brighteners,[21] photochromatic agents,[22] and laser dyes.[23,24] These have generated interest to develop various methods to synthesize 2-substituted benzoxazoles by adopting different synthetic strategies (Scheme 1).[25–34] These methodologies suffer from the limitations of the preparation/availability of starting materials (*ortho* esters, 2-hydroxy/halo/acyloxyanilides, seleno esters/amides, acid chlorides/fluorides), use of excess of reagents (Lawssen's reagent, polyphosphoric acid (PPA), pyridinium-*p*-toluenesulfonate (PPTS), *p*-TsOH, HF, PPh_3, CBr_4, diethyl azodicarboxylate (DEAD), 1,1′-carbonyldiimidazole (CDI), *N*-hydroxybenzotriazole (HOBT), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU), tri-*n*-butylphosphine (TBP), *N*,*N*-di-*iso*-propylethylamine (DIPEA), Deoxo-Fluor, $Mn(OAc)_3$, $Pb(OAc)_4$ or PbO_2, NiO_2, $BaMnO_4$, MnO_2-SiO_2, $PhI(OAc)_2$, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), thianthrene cation radical perchlorate ($Th^{+\bullet}ClO_4^-$), ionic liquids, metal catalysts, etc.), tedious reaction conditions (heating in a sealed tube under microwave), long reaction times, and are applicable to the synthesis of 2-aryl substituted benzoxazoles (except in a few cases). Many of these methodologies require stoichiometric amounts of metal catalysts/oxidants that generate harmful waste products. Some of the reagents used are corrosive in nature (e.g., HF). The use of metal catalysts (employed in the radical/oxidative cyclization reactions) raises concerns of contamination of the product with trace amounts of metallic impurities that are detrimental for the determination of biological activity of the synthesized benzoxazoles. Thus, a convenient synthesis of benzoxazoles is still in demand, and herein we report a one-pot synthesis of 2-substituted benzoxazoles directly from carboxylic acids.

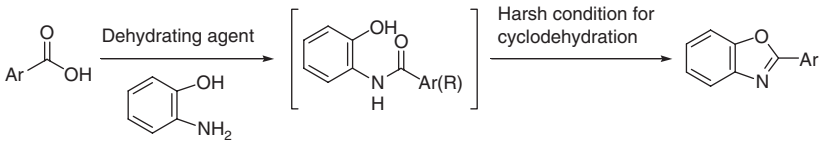


Scheme 1. Various synthetic strategies for the construction of the benzoxazole moiety.

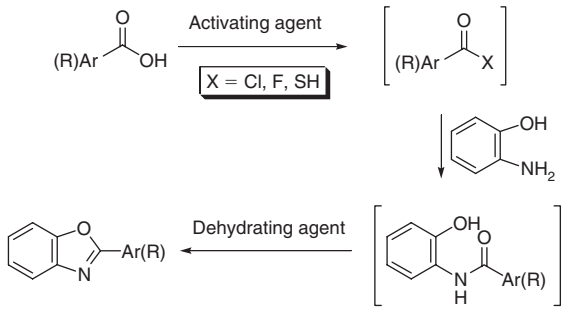
Results and Discussion

In a continuation of our interest in the development of new synthetic methodologies for benzazoles,[34–37] we thought that a direct condensation of carboxylic acids with 2-aminophenols would be a better choice. However, the poor leaving group property of the hydroxy group necessitates the requirement of stoichiometric amounts of dehydrating agents such as PPA/PPTS and stringent reaction conditions (heating at high temperature or in a sealed tube under microwave irradiation) for the intermediate formation of 2-hydroxyanilide and its subsequent cyclodehydration to construct the benzoxazole moiety (Scheme 2). Thus, we recently employed microwave heating for the synthesis of

 10.1071/CH08193 0004-9425/08/110881



Scheme 2. Route of benzoxazole synthesis from carboxylic acids.



Scheme 3. Intermediates involved during benzoxazole synthesis from carboxylic acids in the presence of various agents.

2-substituted benzoxazoles by a direct condensation of carboxylic acids with 2-aminophenol.[34] However, the evaporative loss of the starting material/product and decarboxylative decomposition of the carboxylic acids led to poor yields in some cases and are limitations of the synthetic potential of this methodology. We thought that in-situ activation of the carboxylic acid might make the hetero-annulation feasible under milder conditions. Only a few methodologies have been reported for a direct synthesis from carboxylic acids and involve the treatment with (i) 2 equiv. of Cl_3CN and 3 equiv. of PS-PPh_3 under microwave heating;[28] (ii) stoichiometric amounts of $SnCl_2$ in dioxan at 180°C for 24 h;[38] (iii) 2.6 equiv. of DIPEA, excess K_2CO_3, and 2.2 equiv. of Deoxo-Fluor for 2–3 h;[29] and (iv) Lawesson's reagent under microwave heating.[25] These procedures involve the in-situ formation of the acid halide/amide/thiocarboxylic acid (Scheme 3). The cyclodehydration of 2-hydroxy anilide to the benzoxazole has recently been reported in carrying out the reaction with 4 equiv. of PPh_3 and 2 equiv. of CBr_4 in MeCN at 60°C for 2 h.[28] Other methods involved (i) the use of TBP and DEAD in tetrahydrofuran (THF) for 16 h;[7] (ii) heating at 230°C under vacuum for 5 h or treatment with 2.5–3 equiv. of *p*-TsOH in xylene under reflux for 32 h;[12,13] and (iii) heating under reflux in xylene in the presence of PPTS.[1,2]

We believed that the reaction of an acid chloride, generated in situ from the carboxylic acid, with 2-aminophenol may form the intermediate 2-hydroxyanilide, and subsequent cyclodehydration in the presence of a suitable acid catalyst should afford the benzoxazole. Thus, the procedure may constitute a synthesis of benzoxazoles in one pot directly from carboxylic acids.

In a model study, benzoyl chloride **1** (2.5 mmol) was treated with 2-aminophenol **2a** (2.5 mmol) at 100°C (oil bath) under neat conditions and also in dioxan (Table 1). However, on each occasion no significant conversion into the desired 2-phenylbenzoxazole **3a** was observed (TLC, gas chromatography mass spectrometry (GC-MS)). To follow the progress of the reactions, aliquots (0.25 mL) of samples were withdrawn from the reaction mixture after 0.5, 1, and 2 h and diluted with MeOH (0.25 mL) to quench the reaction. The residues obtained after removal of the volatile components under reduced pressure were subjected to TLC, IR, and GC-MS analyses. In case of the reactions carried out under neat conditions, **2a** and **1** remained unchanged as determined by TLC and IR/GC-MS (formation of methyl benzoate in the case of dilution of the sample with MeOH), and no significant amount of formation of **3a** was observed (TLC, GC-MS). Although the reactions carried out in dioxan indicated the formation

Table 1. Synthesis of 2-phenylbenzoxazole 3a by the reaction of benzoyl chloride 1 with 2-aminophenol 2a in the presence of various protic acids[A]

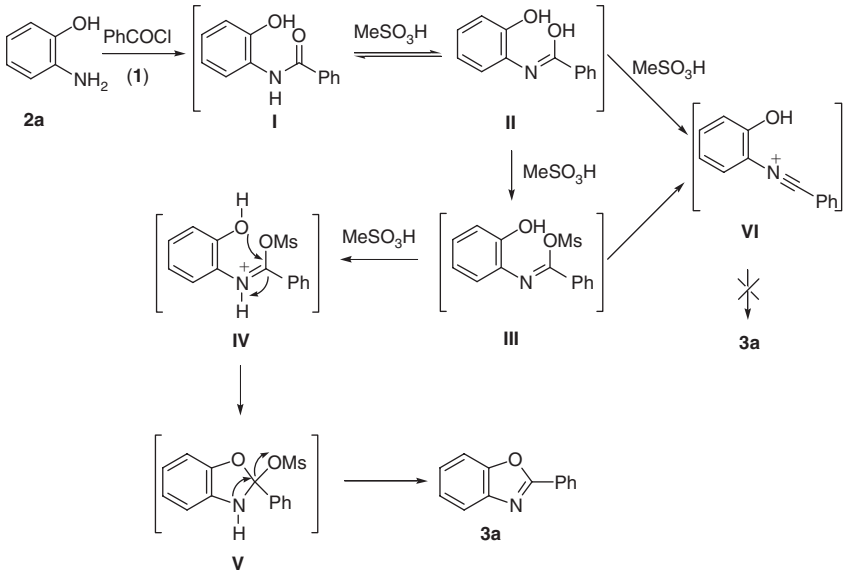
Entry	Protic acid	Amount [mL (mmol)]	Time [h]	Yield[B,C] [%]
1	$MeSO_3H$	4	12	Nil[D]
2	$MeSO_3H$	2	1	94
3	$MeSO_3H$	1 (15.4)	2	96
4	$MeSO_3H$	0.5 (7.7)	2	95
5	$MeSO_3H$	0.25 (3.85)	4	40
6	F_3CSO_3H	0.5 (5.65)	2	91
7	*p*-TsOH	2.5	4	35
8	$HClO_4$ (68% aq.)	2 (13.53)	12	65
9	HCl (conc.)	2 (65.75)	12	65
10	HBr (48% aq.)	2 (11.85)	8	80
11	H_2SO_4 (conc.)	1 (18.76)	12	50
12	HBF_4 (50% aq.)	1 (5.69)	12	30
13	Nil	–	12	Nil[E]
14	Nil	–	12	Nil[E,F]

[A]A mixture of **1** (2.5 mmol) and **2a** (2.5 mmol, 1 equiv.) in dioxan (5 mL) was heated at 100°C (oil bath) in the presence of various protic acids.
[B]Yield of **3a** obtained after purification by column chromatography.
[C]The products were characterized by IR and NMR spectroscopies, and MS.
[D]The reaction was carried out at room temperature.
[E]The reaction mixture contained unreacted **2a** (TLC) and amide (IR).
[F]The reaction was carried out under neat conditions.

Table 2. Synthesis of 2-phenylbenzoxazoles by the reaction of benzoyl chloride 1 with 2-aminophenol 2a in the presence of $MeSO_3H$ in various solvents[A]

Entry	Solvent	Time [h]	Yield[B,C] [%]
1	Dioxan	2	95
2	Xylene	2	89
3	Toluene	4	78
4	THF	4	83
5	MeCN	4	55
6	DMF	4	50
7	DCE	4	45
8	Neat	12	Nil[D]

[A]A mixture of **1** (2.5 mmol) and **2a** (2.5 mmol, 1 equiv.) in dioxan (5 mL) was heated at 100°C (oil bath) in the presence of $MeSO_3H$ (0.5 mL, 7.7 mmol, 3 equiv.).
[B]Yield of 2-phenylbenzoxazole **3a** obtained after purification by column chromatography.
[C]The product was characterized by IR and NMR spectroscopies, and MS.
[D]The 2-hydroxybenzanilide is formed (TLC, IR) and remained unchanged.



Scheme 4. The role of $MeSO_3H$ in benzoxazole formation during the reaction of PhCOCl with **2a**.

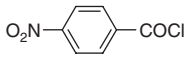
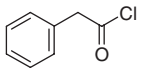
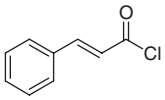
of the amide (IR), no detectable (TLC, GC-MS) amounts of **3a** were formed even after carrying out the reaction for 12 h. These observations suggested the need to use a cyclodehydrating agent to convert the intermediate 2-hydroxyanilide into the benzoxazole. Reported methodologies require stoichiometric quantities of costly reagents[1,2,7,12,13,25,28] and harsh reaction conditions[12,13] that might induce polymerization.[39] Thus, we planned to use easily available protic acids as catalysts and we were delighted to observed that **3a** was formed in 95% yield when carrying out the reaction of **1** (2.5 mmol) with **2a** (2.5 mmol) in the presence of $MeSO_3H$ (0.5 mL, 7.7 mmol, 3 equiv.) for 2 h. Lesser yields were obtained when using smaller amounts (0.25 mL) of $MeSO_3H$. The use of other protic acids afforded inferior results. However, the use of stronger protic acids such as F_3CSO_3H afforded comparable results (entry 6, Table 1). The reported procedures for the formation of 2-hydroxyanilide by the reaction of **2a** with acid halide required the presence of bases such as triethylamine (TEA)[40] or pyridine.[12] However, the use of base may be detrimental for substrates that bear α-hydrogen atoms due to ketene formation. The methodologies reported for the cyclocondensation of acid halides with **2a** to form benzoxazoles required either microwave-assisted dielectric heating[41] or the use of stoichiometric amounts of ionic liquids.[42] However, ionic liquids are in general costly, and the combustibility[43] and corrosion behaviour[44] of several ionic liquids raise concerns over the safety of their use.

To understand the pathway of the benzoxazole formation during the $MeSO_3H$ promoted reactions of **2a** with PhCOCl, aliquots of the sample (0.25 mL) were withdrawn from the reaction mixture after 0.5, 1, and 2 h, diluted with MeOH (0.25 mL) to quench the reaction, and concentrated under reduced pressure. The crude mixtures were subjected to TLC, IR, and GC-MS analyses. The amide formation was complete after 1 h. However, GC-MS revealed that concomitant formation of **3a** takes place after 0.5 h of the addition of the catalyst. This indicates that perhaps the 2-hydroxyanilide formation is also catalyzed by $MeSO_3H$.

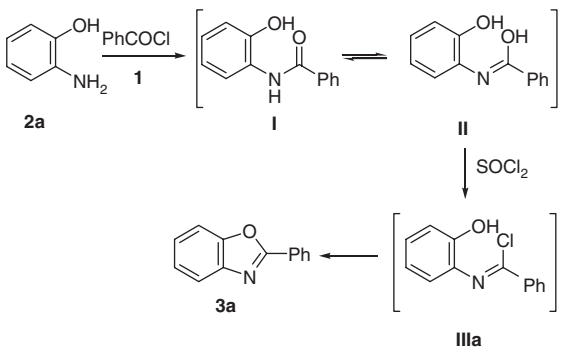
To evaluate the effect of solvent, the reaction was carried out using other solvents (Table 2). The replacement of dioxan with xylene afforded comparable yields but the use of toluene or THF required longer times and afforded lower yields. Inferior results were obtained in using MeCN, *N*,*N*-dimethylformamide (DMF), and 1,2-dichloroethane (DCE) as solvents. No benzoxazole formation took place under neat conditions (TLC, IR). Although dioxan and xylene afforded similar yields, in subsequent studies the reactions were carried out in dioxan to avoid the difficulties in removing high-boiling xylene. The requirement of excess amounts (3 equiv.) of $MeSO_3H$ for the cyclocondensation of the 2-hydroxyanilide to form the benzoxazole led us to believe that perhaps $MeSO_3H$ is involved in covalent bond formation with the intermediate 2-hydroxyanilide to provide a better leaving group to make the cyclocondensation facile (Scheme 4). The in-situ generated 2-hydroxybenzanilide **I** undergoes an amide–imine tautomeric change, perhaps catalyzed by $MeSO_3H$. The iminol **II** reacts with $MeSO_3H$ to form the corresponding mesylate **III**. Protonation of **III** with $MeSO_3H$ forms the immonium ion **IV** that undergoes intramolecular nucleophilic attack by the 2-hydroxy group to form the tetrahedral intermediate **V** followed by elimination of the $MeSO_3^-/MeSO_3H$, which results in the formation of the benzoxazole **3a**. An alternate pathway that involves the intermediacy of the nitrilium ion **VI** arising either by a direct $MeSO_3H$ catalyzed/assisted elimination of water from **II** or of $MeSO_3^-$ from **III** appears unlikely as the linear configuration of the phenylnitrilium moiety in **VI** does not offer appropriate orientation/geometry for approach of the 2-hydroxy group for nucleophilic attack at the benzylic position of the phenylnitrilium moiety.

To determine whether the methodology is applicable to other acid chlorides, commercially available 4-nitrobenzoyl chloride, phenylacetyl chloride, and cinnamoyl chloride were considered as representative electron-deficient aromatic, aryl alkyl, and α,β-unsaturated acid chlorides, respectively, and treated with **2a** in dioxan at 100°C (oil bath) in the presence of $MeSO_3H$ (Table 3). In each case, the corresponding benzoxazole was obtained in excellent yields. No competitive side reactions such as aromatic nucleophilic substitution (of the nitro group in case of 4-nitrobenzoyl chloride), ketene formation (in case of phenylacetyl chloride), or conjugate addition (in case of cinnamoyl chloride) took place.

Table 3. Synthesis of benzoxazoles by the reaction of 2a with various acid chlorides[A]

Entry	Acid chloride	Time [h]	Yield[B,C] [%]
1		2	92
2		2	95
3		3	95

[A]The acid chloride (2.5 mmol) was treated with **2a** (2.5 mmol, 1 equiv.) in dioxan (5 mL) at 100°C (oil bath) in the presence of $MeSO_3H$ (0.5 mL, 7.7 mmol, 3 equiv.).
[B]Yield of the benzoxazole obtained after purification by column chromatography.
[C]The product was characterized by IR and NMR spectroscopies, and MS.

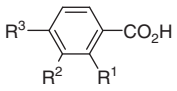
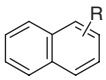
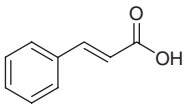
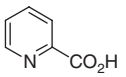
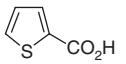
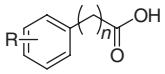
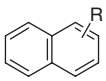
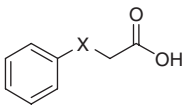


Scheme 5. Benzoxazole formation during the reaction of in-situ generated and commercially available PhCOCl with **2a** in the presence of $SOCl_2$.

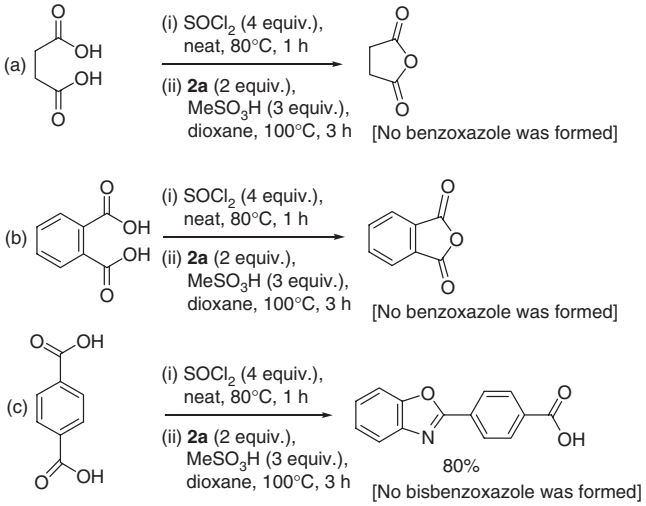
Encouraged by the above results, we further realized that the lack of commercially available acid chlorides may limit the generality and is a notable drawback of the reported procedures.[41,42] Thus, we thought of a direct and one-pot conversion of carboxylic acids into the corresponding benzoxazoles by in-situ generation of the acid chloride. In a model study, phenylacetic acid (2.5 mmol) was treated with $SOCl_2$ (3.0 mmol, 1.2 equiv.) under neat conditions at 80°C so as to generate the phenylacetyl chloride. The reaction was monitored for the consumption of phenylacetic acid (TLC) as well as the formation of the acid chloride by taking out an aliquot (0.25 mL) of sample from the reaction mixture, quenching with MeOH (0.25 mL), followed by TLC and GC-MS and comparing with an authentic sample of methyl phenylacetate that ensured the in-situ formation of the acid chloride. After the complete consumption of phenyl acetic acid (1 h), the excess $SOCl_2$ was distilled off and the residue was treated with **2a** in dioxan (5 mL) in the presence of $MeSO_3H$ (0.5 mL) for 2 h at 100°C (oil bath). After the usual workup, the benzoxazole was obtained in 95% yield. We observed that the acid chloride formation takes place in a shorter time (0.5 h) when using PhMe as solvent. However, it was preferred to adopt the in-situ acid chloride formation under neat conditions when considering the requirement of a longer reaction time for the subsequent step (Table 2, entry 3) and to avoid the difficulty in the removal of PhMe.

We presumed that the use of $SOCl_2$ instead of $MeSO_3H$ may generate the α-chloroimine **IIIa** (which corresponds to the mesylate **III** in Scheme 4) and enable formation of **3a** by intramolecular nucleophilic displacement of the chlorine by the 2-hydroxy group (Scheme 5). Thus, in separate experiments, the in-situ generated (prepared by the treatment of $PhCO_2H$ with 1.5 equiv. of $SOCl_2$ at 80°C for 1 h under neat conditions) and commercially available PhCOCl were treated with **2a** in the presence of an additional amount (3 equiv.) of $SOCl_2$ in dioxan at 100°C. Although in both cases **3a** was formed after 4 h (TLC), significant amounts of 2-hydroxybenzanilide

Table 4. One-pot synthesis of benzoxazoles directly from aryl, heteroaryl, and arylalkyl carboxylic acids[A]

Entry	Acid	Time [h]	Yield[B,C] [%]
			
1	$R^1 = R^2 = R^3 = H$	2	95[D]
2	$R^1 = R^2 = H$; $R^3 = Cl$	2	70
3	$R^1 = Cl$; $R^2 = R^3 = H$	2	60
4	$R^1 = Br$; $R^2 = R^3 = H$	2	70
5	$R^1 = R^2 = H$; $R^3 = NO_2$	2	90
6	$R^1 = H$; $R^2 = OC_5H_9$-*c*; $R^3 = OMe$	3	85
			
7	R = 1-CO_2H	2	90
8	R = 2-CO_2H	2	82
9		3	92
10		2	85
			
11		2	82
12	R = H, *n* = 1	2	95
13	R = 3-OMe, *n* = 1	2	95
14	R = H, *n* = 2	2	90
			
15	R = 1-CH_2CO_2H	2	90
16	R = 2-CH_2CO_2H	2	90
			
17	X = O	2.5	80
18	X = S	2	92

[A]The carboxylic acid (2.5 mmol) was treated with $SOCl_2$ (3.0 mmol, 1.2 equiv.) at 80°C for 1 h, followed by distilling off the excess of $SOCl_2$ and treatment with **2a** (2.5 mmol, 1 equiv.) in the presence of $MeSO_3H$ (0.5 mL, 7.7 mmol, 3 equiv.) in dioxane with heating at 100°C (oil bath).
[B]Yield of the benzoxazole obtained after purification by column chromatography.
[C]The product was characterized by IR and NMR spectroscopies, and MS.
[D]The product was formed in 89% yield by carrying out the reaction with F_3CSO_3H (0.5 mL).



Scheme 6. Reaction of dicarboxylic acids with $SOCl_2$ followed by the treatment with **2a** in the presence of $MeSO_3H$.

remained unreacted. These observations further supported the role of $MeSO_3H$ in the cyclodehydration/hetero-annulation step.

To establish generality, various aromatic, heteroaromatic, styryl, and arylalkyl carboxylic acids were subjected to this procedure. Since comparable results are obtained when using $MeSO_3H$ and F_3CSO_3H, the reactions were carried out using $MeSO_3H$ as it is easily available, less costly, and easier to handle compared with F_3CSO_3H. In each case the corresponding benzoxazoles were formed in excellent yields (Table 4). The procedure was compatible with various substituents such as halogen atoms, alkoxy, phenoxy, thiophenoxy, nitro, and α,β-unsaturated carboxylic acid groups. No nucleophilic substitution of the halogen atom (entries 2–4, Table 4) or the nitro group (entry 5, Table 4) and aza-/oxa-Michael addition to an α,β-unsaturated carbonyl moiety (entry 9, Table 4) were observed. Chemoselective benzoxazole formation took place with phenoxy/thiophenoxy acetic acids (entries 17 and 18, Table 4), with no competitive nucleophilc substitution of the phenoxy/thophenoxy moiety.

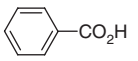
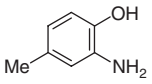
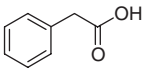
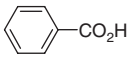
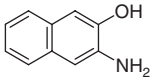
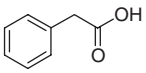
We next extended this procedure to dicarboxylic acids such as succinic acid, phthalic acid, and terephthalic acid so as to prepare the corresponding bisbenzoxazoles (Scheme 6). In the case of phthalic acid and succinic acid, no benzoxazole was obtained and instead the corresponding anhydrides were formed. In the case of terephthalic acid the corresponding monobenzoxazole was the only product formed. The bisbenzoxazole was not formed even after the use of excess of $SOCl_2$ and 4 equiv. of **2a** or the treatment of the isolated monobenzoxazole separately with $SOCl_2$ and **2a**.

To claim the generality with respect to substituted 2-aminophenols, a few representative aryl and arylalkyl carboxylic acids were subjected to benzoxazole formation with 4-methyl-2-aminophenol **2b** and 3-amino-2-naphthol **2c** following this procedure (Table 5). The corresponding benzoxazoles were formed in 82–87% yields.

Conclusions

In conclusion, we have developed a convenient synthesis of benzoxazoles by the reaction of acid chlorides, generated in situ from carboxylic acids, with 2-aminophenols catalyzed by $MeSO_3H$. The feasibility of the cyclocondensation of 2-aminophenol with acid chlorides, generated in situ from carboxylic acids, in one pot demonstrates a direct synthesis of 2-substituted benzoxazoles from carboxylic acids. Benzoxazole formation was found to be applicable to a large variety of substrates such as aryl, heteroaryl, and arylalkyl carboxylic acids as well as substituted 2-aminophenols. The compatibility of the reaction conditions with various substituents (e.g., chloro, bromo, nitro, methoxy, cyclopentyloxy, phenoxy, thiophenoxy, and conjugated double bonds) demonstrates chemoselectivity.

Table 5. One-pot synthesis of benzoxazoles from 4-methyl-2-aminophenol 2b and 3-amino-2-naphthol 2c[A]

Entry	Acid	Aminophenol	Time [h]	Yield[B,C] [%]
1			3	85
2			2.5	85
3			2	87
4			2	82

[A]The carboxylic acid (2.5 mmol) was treated with $SOCl_2$ (3.0 mmol, 1.2 equiv.) at 80°C for 1 h, followed by distilling off the excess of $SOCl_2$ and treatment with **2b** or **2c** (2.5 mmol, 1 equiv.) in the presence of $MeSO_3H$ (0.5 mL, 7.7 mmol, 3 equiv.) in dioxan under heating at 100°C (oil bath).
[B]Yield of the benzoxazole obtained after purification by column chromatography.
[C]Characterized by IR and NMR spectroscopies, and MS.

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 300 (300 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. IR spectra were recorded on Nicolet Impact 400 spectrometer as KBr pellets for solid samples and neat for liquid samples. Mass spectra were recorded on a QCP 5000 (Shimadzu) GCMS. The reactions were monitored by TLC (Merck). Evaporation of solvents was performed under reduced pressure using a Büchi rotary evaporator. Methanesulfonic acid, 1-naphthoic acid, 2-naphthoic acid, 1-naphthaleneacetic acid, 2-naphthaleneacetic acid, terephthalic acid, *trans*-cinnamic acid, phenoxyacetic acid, thiophenoxyacetic acid, and 4-methyl-*o*-phenylendiamine were procured from Aldrich, India. Benzoic acid, 4-chlorobenzoic acid, 2-chlorobenzoic acid, 2-bromobenzoic acid, 2-thiophenecarboxylic acid, and succinic acid were purchased from Loba chemie pvt. Ltd., India. Benzoyl chloride and phthalic acid were purchased from s d fine-chem Ltd., India. 4-Nitrobenzoic acid, cinnamoyl chloride, and pyridine-2-carboxylic acid were from Merck, India.

Representative Procedure for the Synthesis of Benzoxazole from Acid Chloride. 2-Phenylbenzoxazole (Table 1, Entry 3)

Benzoyl chloride **1** (348 mg, 2.5 mmol) was treated with 2-aminophenol **2a** (272 mg, 2.5 mmol, 1 equiv.) in dioxan (5 mL) followed by addition of CH_3SO_3H (0.5 mL, 7.7 mmol, 3 equiv.).

The resultant mixture was stirred magnetically at 100°C (oil bath). After complete consumption of **2a** (2 h, TLC), the dioxan was removed by rotary evaporation under reduced pressure and the residue was diluted with EtOAc (10 mL) followed by saturated aq. $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with H_2O (3 × 5 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to afford 2-phenylbenzoxazole **3a** (463 mg, 95%), analytically identical (mp, IR, NMR, and MS) with an authentic sample.[34] ν_{max} (neat)/cm^{-1} 2920, 1620, 1545, 1245. δ_H (300 MHz, $CDCl_3$) 7.33–7.37 (m, 2H), 7.51–7.54 (m, 3H), 7.56–7.59 (m, 1H), 7.77–7.79 (m, 1H), 8.25–8.27 (m, 2H). δ_C (75 MHz, $CDCl_3$) 110.6, 120.0, 124.6, 125.1, 127.2, 127.6, 128.9, 131.5, 142.1, 150.7, 163.0. *m/z* (APCI) 196.2 (MH^+).

Representative Procedure for a Direct One-Pot Synthesis of Benzoxazole from Carboxylic Acid. 2-Benzylbenzoxazole (Table 4, Entry 12)

Phenylacetic acid (340 mg, 2.5 mmol) was treated with $SOCl_2$ (357 mg, 3.0 mmol, 0.22 mL, 1.2 equiv.) at 80°C until quenching of an aliquot with a few drops of MeOH revealed the complete consumption of phenylacetic acid and appearance of a new spot (methyl phenylacetate) by TLC (1 h). The excess $SOCl_2$ was distilled off and the reaction mixture was treated with **2a** (272 mg, 2.5 mmol) in dioxan (5 mL) followed by addition of CH_3SO_3H (0.5 mL). The resultant mixture was stirred magnetically at 100°C (oil bath). After complete consumption of **2a** (2 h, TLC), the dioxan was removed by rotary evaporation and the residue was diluted with EtOAc (10 mL) followed by saturated aq. $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with H_2O (3 × 5 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to afford 2-benzylbenzoxazole (496 mg, 95%), analytically identical (mp, IR, NMR, and MS) to an authentic sample.[34] ν_{max} (neat)/cm^{-1} 3019, 1589, 1405, 1215. δ_H (300 MHz, $CDCl_3$) 7.64–7.70 (m, 1H), 7.41–7.46 (m, 1H), 7.23–7.39 (m, 7H), 4.25 (s, 2H). δ_C (75 MHz, $CDCl_3$) 165.1, 151.0, 141.3, 134.7, 126.8, 127.3, 124.6, 124.1, 119.8, 110.4, 35.2. *m/z* (APCI) 210 (MH^+). The remaining reactions were carried out following this general procedure. The physical data (mp, IR, NMR, and MS) of the known compounds were in complete agreement with those of authentic samples. The following compounds are new.

2-(2-Cyclopentyloxy-4-methoxy)phenylbenzoxazole (Table 4, Entry 6)

White solid, mp 80–82°C. ν_{max} (KBr)/cm^{-1} 2949, 2865, 2360, 2032, 1618, 1555, 1501, 1441, 1362, 1274, 1259, 1170. δ_H (300 MHz, $CDCl_3$) 7.79 (d, *J* 17.40, 3H), 7.55 (s, 1H), 7.32 (s, 2H), 6.97 (s, 1H), 3.93 (s, 3H), 1.94 (d, *J* 19.38, 6H), 1.66 (s, 2H). δ_C (75 MHz, $CDCl_3$) 163.8, 153.6, 148.5, 142.9, 124.9, 24.7, 125.5, 121.6, 113.9, 120.1, 112.1, 110.9, 81.2, 56.6, 33.4. *m/z* (APCI) 310.5 (MH^+). (Found: C 73.74, H 6.20, N 4.55. Calc. for $C_{19}H_{19}NO_3$: C 73.77, H 6.19, N 4.53%.)

3-Benzyl-naphtho[2,3-d]oxazole (Table 5, Entry 4)

White solid, mp 140–142°C. ν_{max} (KBr)/cm^{-1} 3733, 3031, 2918, 2360, 1961, 1611, 1574, 1454, 1417, 1396, 1242, 1261, 1214, 1145, 1134, 956, 904, 873, 904, 845, 752, 718, 690, 480. δ_H (300 MHz, $CDCl_3$) 8.11 (s, 1H), 7.89–7.99 (m, 2H), 7.83 (s, 1H), 7.25–7.48 (m, 7H), 4.31 (s, 2H). δ_C (75 MHz, $CDCl_3$) 168.1, 150.5, 141.9, 135.0, 132.0, 131.8, 129.7, 129.5, 129.0, 128.4, 128.0, 126.0, 125.2, 117.7, 106.9, 36.0. *m/z* (APCI) 260.5 (MH^+). (Found: C 83.37, H 5.05, N 5.40. Calc for $C_{18}H_{13}NO$: C 83.35, H 5.08, N 5.44%.)

Reaction with Dicarboxylic Acids. 4-Benzooxazol-2-ylbenzoic Acid (Scheme 6)

Terephthalic acid (0.41 g, 2.5 mmol) was treated with $SOCl_2$ (357 mg, 0.22 mmol, 1.2 equiv.) at 80°C until quenching an aliquot with a few drops of MeOH revealed the complete consumption of terephthalic acid and the appearance of a new spot (methyl ester) by TLC (2 h). Excess $SOCl_2$ was removed and the reaction mixture was treated with **2a** (272 mg, 2.5 mmol) in dioxan (5 mL) and CH_3SO_3H (0.5 mL, 7.7 mmol, 3 equiv.) by heating under reflux for 3 h. After completion of the reaction, dioxan was removed under rotary evaporation. The residue was diluted with EtOAc (10 mL) and treated with saturated aq. $NaHCO_3$ (5 mL). The organic layer was separated and washed with H_2O (3 × 5 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to afford the title compound (0.47 g, 80%). White solid, mp 303°C. ν_{max} (KBr)/cm^{-1} 3802, 3451, 2999, 2542, 2363, 2068, 1683, 1603, 1576, 1449, 1242. δ_H (300 MHz, $CDCl_3$) 8.33 (d, *J* 8.2, 2H), 8.16 (d, *J* 8.2, 2H), 7.83 (m, 2H), 7.49 (m, 2H). *m/z* (APCI) 240.2 (MH^+). (Found: C 70.29, H 3.79, N 5.86. Calc for $C_{14}H_9NO_3$: C 70.32, H 3.78, N 5.85%.)

Acknowledgements

The author (S.R.) thanks DST, New Delhi, India, for the award of Senior Research Fellowship.

References

[1] L.-Q. Sun, J. Chen, M. Bruce, J. A. Deskus, J. R. Epperson, K. Takaki, G. Johnson, L. Iben, C. D. Mahle, E. Ryan, C. Xu, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3799. doi:10.1016/J.BMCL.2004.04.082

[2] L.-Q. Sun, J. Chen, K. Takaki, G. Johnson, L. Iben, C. D. Mahle, E. Ryan, C. Xu, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1197. doi:10.1016/J.BMCL.2003.12.052

[3] P. L. López-Tudanca, L. Labeaga, A. Innerárity, L. Alonso-Cires, I. Tapia, R. Mosquera, A. Orjales, *Bioorg. Med. Chem.* **2003**, *11*, 2709. doi:10.1016/S0968-0896(03)00243-8

[4] L. S. Lin, T. J. Lanza, L. A. Castonguay, Jr, T. Kamenecka, E. McCauley, G. V. Riper, L. A. Egger, R. A. Mumford, X. Tong, M. MacCoss, J. A. Schmidt, W. K. Hagmann, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2331. doi:10.1016/J.BMCL.2004.01.098

[5] C. Lai, R. J. Gum, M. Daly, E. H. Fry, C. Hutchins, C. Abad-Zapatero, T. W. von Geldern, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1807. doi:10.1016/J.BMCL.2006.01.014

[6] S. M. Sondhi, N. Singh, A. Kumar, O. Lozach, L. Meijer, *Bioorg. Med. Chem.* **2006**, *14*, 3756.

[7] D. Berta, M. Villa, A. Vulpetti, E. R. Felder, *Tetrahedron* **2005**, *61*, 10801. doi:10.1016/J.TET.2005.08.070

[8] M. Medebielle, S. Ait-mohand, C. Burkhloder, Jr, W. R. Dolbier, G. Laumond, A.-M. Aubertin, *J. Fluor. Chem.* **2005**, *126*, 533. doi:10.1016/J.JFLUCHEM.2004.12.016

[9] B. Gong, F. Hong, C. Kohm, L. Bonham, P. Klein, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1455. doi:10.1016/J.BMCL.2004.01.023

[10] R. Paramashivappa, P. P. Kumar, P. V. Subba Rao, A. Srinivasa Rao, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 657. doi:10.1016/S0960-894X(02)01006-5

[11] P. D. Edwards, E. F. Meyer, J. J. Vijayalakshmi, P. A. Tuthill, D. A. Andisik, B. Gomes, A. Strimpler, *J. Am. Chem. Soc.* **1992**, *114*, 1854. doi:10.1021/JA00031A046

[12] S.-T. Huang, I.-J. Hsei, C. Chen, *Bioorg. Med. Chem.* **2006**, *14*, 6119.

[13] D. Kumar, M. R. Jacob, M. B. Reynolds, S. M. Kerwin, *Bioorg. Med. Chem.* **2002**, *10*, 3997. doi:10.1016/S0968-0896(02)00327-9

[14] I. I. Rodríguez, A. D. Rodríguez, Y. Wang, S. G. Franzblau, *Tetrahedron Lett.* **2006**, *47*, 3229. doi:10.1016/J.TETLET.2006.03.048
[15] J. Kočí, V. Klimešová, K. Waisser, J. Kaustová, H.-M. Dahse, U. Möllmann, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3275. doi:10.1016/S0960-894X(02)00697-2
[16] Ö. Temiz, İ. Ören, E. Şener, İ. Yalçin, N. Uçarturk, *IL Farmaco* **1998**, *53*, 337 and references cited therein. doi:10.1016/S0014-827X(98)00030-5
[17] A. Kumar, D. Kumar, *ARKIVOC* **2007**, 117.
[18] J. Vinsova, K. Cermakova, A. Tomeckova, M. Ceckova, J. Jampilek, P. Cermak, J. Kunes, M. Dolezal, F. Staud, *Bioorg. Med. Chem.* **2006**, *14*, 5850. doi:10.1016/J.BMC.2006.05.030
[19] S. M. Rida, F. A. Ashour, S. A. M. El-Hawash, M. M. ElSemary, M. M. M. Badr, M. H. Shalaby, M. A. Shalaby, *Eur. J. Med. Chem.* **2005**, *40*, 949. doi:10.1016/J.EJMECH.2005.03.023
[20] I. Yildiz-Oren, I. Yalcin, E. Aki-sener, N. Ucarturk, *Eur. J. Med. Chem.* **2004**, *39*, 291. doi:10.1016/J.EJMECH.2003.11.014
[21] S.-I. Um, *Dyes Pigments* **2007**, *75*, 185. doi:10.1016/J.DYEPIG.2006.04.024
[22] P.-E. Sum, D. How, N. Torres, H. Newman, P. J. Petersen, T. K. Mansour, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2607. doi:10.1016/S0960-894X(03)00512-2
[23] A. Heynderickx, R. Guglielmetti, R. Dubest, J. Aubard, A. Samat, *Synthesis* **2003**, 1112.
[24] A. V. Eltsov (Ed.), *Organic Photochromes* **1990**, p. 178 (Plenum Press: New York, NY).
[25] J. A. Seijas, M. P. Vázquez-Tato, M. R. Carballido-Reboredo, J. Crecente-Campo, L. Romar-López, *Synlett* **2007**, 313. doi:10.1055/S-2007-967994
[26] I. Mohammadpoor-Baltork, A. R. Khosropour, S. F. Hijati, *Monatsh. Chem.* **2007**, *138*, 663.
[27] G. Evindar, R. A. Batey, *J. Org. Chem.* **2006**, *71*, 1802. doi:10.1021/JO051927Q
[28] Y. Wang, K. Sarris, D. R. Sauer, S. W. Djuric, *Tetrahedron Lett.* **2006**, *47*, 4823. doi:10.1016/J.TETLET.2006.05.052
[29] C. O. Kangani, D. E. Kelley, B. W. Day, *Tetrahedron Lett.* **2006**, *47*, 6497. doi:10.1016/J.TETLET.2006.07.032
[30] Y.-H. Yang, M. Shi, *Tetrahedron* **2006**, *62*, 2420. doi:10.1016/J.TET.2005.11.077
[31] D. Alagille, R. M. Baldwin, G. D. Tamagnan, *Tetrahedron Lett.* **2005**, *46*, 1349. doi:10.1016/J.TETLET.2004.12.111
[32] L. Bréhu, A.-C. Fernandes, O. Lavergne, *Tetrahedron Lett.* **2005**, *46*, 1437. doi:10.1016/J.TETLET.2005.01.045
[33] L. F. Olguín, M. Jiménez-Estrada, E. Bárzana, *Synlett* **2005**, 340.
[34] R. Kumar, C. Selvam, G. Kaur, A. K. Chakraborti, *Synlett* **2005**, 1401 and the references therein.
[35] S. Rudrawar, A. Kondaskar, A. K. Chakraborti, *Synthesis* **2005**, 2521.
[36] A. K. Chakraborti, S. Rudrawar, L. Sharma, G. Kaur, *Synlett* **2004**, 1533. doi:10.1055/S-2004-829089
[37] A. K. Chakraborti, C. Selvam, G. Kaur, S. Bhagat, *Synlett* **2004**, 851. doi:10.1055/S-2004-820012
[38] C. S. Cho, D. T. Kim, J. Q. Zhang, S.-L. Ho, T.-J. Kim, S. C. Shim, *J. Heterocycl. Chem.* **2002**, *39*, 421.
[39] R. Hoogenboom, F. Weisbrock, M. A. M. Leenen, M. Van der Loop, S. F. G. M. Van Nispen, U. S. Schubert, *Aust. J. Chem.* **2007**, *60*, 656. doi:10.1071/CH07150
[40] C. Chen, Y.-J. Chen, *Tetrahedron Lett.* **2004**, *45*, 113. doi:10.1016/J.TETLET.2003.10.095
[41] R. S. Pottorf, N. K. Chadha, M. Katkevics, V. Ozola, E. Suna, H. Ghane, T. Regberg, M. R. Player, *Tetrahedron Lett.* **2003**, *44*, 175. doi:10.1016/S0040-4039(02)02495-4
[42] R. N. Nadaf, S. A. Siddiqui, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *J. Mol. Catal. A: Chem.* **2004**, *214*, 155. doi:10.1016/J.MOLCATA.2003.10.064
[43] M. Smiglak, W. M. Reichert, J. D. Holbrey, J. S. Wilkes, L. Sun, J. S. Thrasher, K. Kirchenko, S. Singh, A. R. Katritzky, R. D. Rogers, *Chem. Commun.* **2006**, 2554. doi:10.1039/B602086K
[44] M. Uerdingen, C. Treber, M. Balser, G. Schmitt, C. Werner, *Green Chem.* **2005**, *7*, 321. doi:10.1039/B419320M